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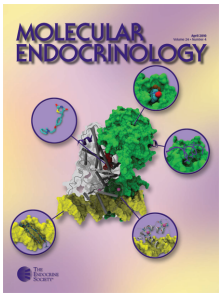

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Panhypopituitarism as a Model to Study the Metabolism of Dehydroepiandrosterone (DHEA) in Humans*

JACQUES YOUNG, BEATRICE COUZINET, KHALIL NAHOUL, SYLVIE BRAILLY, PHILIPPE CHANSON, ETIENNE EMILE BAULIEU, AND GILBERT SCHAISON

Service d'Endocrinologie et des Maladies de la Reproduction, (J.Y., B.C., K.N., P.C., G.S.), Laboratoire de Biochimie Hormonale (S.B.); Inserm U 33 (E.E.B.) and IFR 21 (J.Y., E.E.B., G.S.), Hopital Bicêtre 94275 Kremlin Bicêtre, France

ABSTRACT

The physiological importance and therapeutical interest of dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) are still controversial. Panhypopituitarism is characterized by the absence of secretion of adrenal and gonadal steroids and thus the production of their metabolites. The conversion of DHEA given orally into Δ5 derivatives, androgens, androgen metabolites, and estrogens was studied in ten patients with complete panhypopituitarism. Sex steroid therapy was withdrawn for at least 2 months. Each patient received, at 1-month intervals and in a random order, two single oral doses of DHEA (50 mg and 200 mg) and placebo. During each treatment, urine samples were collected for 24 h, and blood samples were drawn at hourly intervals for 8 h. In patients with pituitary deficiency, plasma DHEA and DHEAS were not detectable and increased, with the 50 mg dose, up to levels observed in young adults. The administration of 200 mg of DHEA induced an increase of both steroids to supraphysiological plasma levels. A small increase of Δ5-androstenediol was observed. In contrast, the increase of plasma Δ4-androstenedione was important and dose dependent. DHEA was also converted into the potent sex steroid testosterone (T). The administration of a 50 mg dose of DHEA restored plasma T to levels similar to those observed in young women. The 200 mg dose induced an important increase of plasma T, sligthly below the levels observed in normal men. The increase of plasma dihydrotestosterone levels was small at both doses of DHEA, in contrast with the large conversion of DHEA into androsterone glucuronide and androstanediol glucuronide. Finally, DHEA administration induced a significant and dose dependent increase of plasma estrogens and particularly of estradiol.

In conclusion, this short term study demonstrates that: 1) panhypopituitarism is a model of interest to study the metabolism of DHEA; 2) in the absence of pituitary hormones and of adrenal and gonadal steroids, DHEA given orally is mainly converted into Δ4 derivatives, which in turn are strongly metabolized into 5α-3keto-reduced steroids; 3) a significant increase of sex active hormones was observed in plasma after 200 and even 50 mg of DHEA. Thus, biotransformation of DHEA into potent androgens and estrogens may explain several of the reported beneficial actions of this steroid in aging people. (*J Clin Endocrinol Metab* **82:** 2578–2585, 1997)

DEHYDROEPIANDROSTERONE SULFATE (DHEAS) is the most abundant steroid hormone in the circulation. However its physiological role and that of its parent steroid, DHEA, remain unknown. Plasma DHEA and DHEAS levels peak at age 25–30 yr and decline thereafter, so that by age 70 yr, plasma levels of these steroids are only 5–10% of what they were during youth (1–3). In contrast, plasma concentrations of cortisol and other adrenal steroids remain relatively unchanged with aging. The fall in plasma concentration of DHEA and DHEAS occurs as the incidence of deleterious metabolic changes and diseases increases, suggesting that higher levels of DHEA and DHEAS may protect against the development of these degenerative processes. Active sex steroids have well documented beneficial effects on age-related deficiencies. Therefore, the question arises whether DHEA has protective effects per se or through transformation into active metabolites.

In normal subjects, conversion of DHEA into active androgens and estrogens has been well documented by using high pharmacological doses of this steroid (1600 mg/day) (4). In contrast, treatment with low doses of DHEA (50 mg/day) induced significant increases in circulating active androgens in women, but not in men of advancing age (5, 6). Thus, beneficial effects observed at these low doses have been assigned to DHEA and/or to its intracrine conversion into active sex steroids (7). However, DHEA metabolism in healthy men and women can be masked by endogenous steroid secretion. Panhypopituitarism, characterized by the absence of secretion of adrenal and gonadal androgens and estrogens as well as the production of their metabolites, is thus a convenient model to study DHEA metabolism and action.

The purpose of the present short-term study was to assess, in this model comparative to placebo, the conversion of a replacement dose (50 mg) and a high dose (200 mg) of oral DHEA into the Δ5 derivatives DHEAS and Δ5-androsten-3β,17β-diol, androgens, androgen metabolites, and estrogens in the absence of these endogenous steroids.

Subjects and Methods

Subjects

Ten patients (six women and four men) with panhypopituitarism participated in the study. The pituitary deficiency was the consequence of hypothalamic or pituitary tumors treated by surgery and/or radiotherapy in nine of them (Table 1). In all patients, the diagnosis was established following pituitary stimulation tests (Table 2). The complete gonadotropic deficiency was confirmed by the association of barely

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Address all correspondence and requests for reprints to: Gilbert Schaison, M.D., Service d'Endocrinologie et des maladies de la Reproduction, Hopital Bicêtre, 94275 Kremlin Bicêtre, France.

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TABLE 1. Characteristics of patients with panhypopituitarism

Patient no.	Age (yr)	Sex	Diagnosis	Treatment
1	53	f	Craniopharyngioma	S, R
2	59	m	NFA	S
3	39	m	NFA	S, R
4	54	f	NFA	S, R
5	61	f	Craniopharyngioma	S, R
6	44	f	NFA	S, R
7	65	m	Craniopharyngioma	S
8	42	m	Craniopharyngioma	S, R
9	32	f	Sarcoidosis	–
10	62	f	NFA	S, R

S, surgery; R, radiation therapy; NFA, Clinically nonfunctional pituitary adenoma.

detectable or undetectable sex steroid plasma levels, with low basal and stimulated (GnRH, 100 μg iv) gonadotropin hormones. Plasma cortisol and ACTH were low and unresponsive to ovine-CRH (o-CRH: 100 μg, iv). Plasma FT_4, FT_3, and TSH (basal and after TRH) levels were low before replacement therapy. Plasma GH levels were not stimulated by GHRH (100 μg, iv). In all patients but one (patient 9), plasma prolactin levels were low and not stimulated by TRH (200 μg iv). All patients gave informed consent for participation in this study, which was approved by the Human Investigation Committee of Paris-Sud University.

Protocol

All patients were studied after withdrawal of testosterone or estrogen and progestin therapy for at least 2 months. Hydrocortisone (20 mg/day) and thyroid hormone replacement therapy were maintained. None of the patients received GH therapy. The study was randomized and placebo controlled. Each patient received in a random order two single oral doses of DHEA (50 mg and 200 mg) or a single oral dose of placebo. Each dose of DHEA or placebo was administered at a minimum interval of 4 weeks. Placebo tablets were identical to DHEA tablets (50 mg). Blood samples were drawn at baseline and at hourly intervals for 8 h. Plasma samples were stored below -20 C until assayed. Twenty-four-hour urine samples were collected during each treatment.

Hormone assays

Plasma steroid levels were determined by radioimmunoassay after chromatographic separation on a sephadex LH 20 or celite column as previously described (8–13). The following steroids were measured: DHEA and DHEAS, Δ5-androsten-3β,17β-diol (Δ5 ADIOL), androsten-3,17-dione (Δ4 ADIONE), testosterone (T), 5α-dihydrotestosterone (DHT), estrone (E_1), and estradiol (E_2). Androstane-3α,17β-diol glucuronide (ADG) and androsterone glucuronide (ADTG) were first hydrolyzed with β-glucuronidase, separated by chromatography, and then radioimmunoassayed (RIA) as nonconjugated steroids as previously described (11). Assay sensitivity was 0.17 nmol/L for DHEA, T, Δ4 ADIONE, DHT, Δ5 ADIOL, ADG, and ADTG, and 0.17 μmol/L for DHEAS. The detection limit for E_1 and E_2 was 25.8 and 18.3 pmol/L respectively. Inter- and intraassay precision coefficients of variation (CV) for these plasma steroid RIAs were 8 and 7.8% for DHEA, 5 and 4.7% for DHEAS, 6.2 and 6% for Δ5 ADIOL, 7.6 and 4.6 for Δ4 ADIONE, 6 and 5.8 for T, 8 and 5.8 for DHT, 13.2 and 10.8 for E_1, 8.5 and 5.1 for E_2. Inter- and intraassay CV were 7 and 5.4% for ADG and 6.8 and 6.2 for ADTG.

Statistical analysis

The data are presented as the mean ± standard error (SE). Statistical significance was considered at $P < 0.05$. Statistical analyses were performed with the nonparametric paired Wilcoxon test for comparison between treatments (14).

Results

All plasma steroid levels measured in untreated patients with panhypopituitarism were low and did not differ between male and female subjects (Table 2). Consequently, data from male and female patients were analyzed simultaneously.

Plasma Δ5 steroids

Plasma DHEA, Δ5 ADIOL, and DHEAS levels were not detectable in these patients with panhypopituitarism. A prompt and dose dependent increase in all these Δ5 steroids occurred after an oral dose of DHEA compared with placebo (Fig. 1). Mean maximal increment in plasma DHEA levels was seen 2 h after DHEA ingestion. With the 50 mg dose, mean plasma DHEA levels reached levels (12.8 ± 1.4 nmol/L) observed in normal young adults. With the 200 mg dose, plasma DHEA levels peaked 4-fold above the peak observed with the 50 mg dose (45.8 ± 4.9 nmol/L). Plasma DHEAS levels increased dramatically 4 h and 3 h after the 50 and the 200 mg doses respectively. With 50 mg of DHEA, mean plasma DHEAS levels increased from 0.15 ± 0.10 to 15.6 ± 2.5 μmol/L and were above the upper values observed in normal young individuals, whereas with 200 mg, the peak was 4-fold more important (41.0 ± 3.7 μmol/L). In contrast, plasma Δ5 ADIOL levels showed a small increase 3 h and 1 h after the 50 and the 200 mg doses respectively (Fig. 1).

Plasma Δ4 steroids and DHT

Plasma Δ4 ADIONE, T, and DHT levels were very low or undetectable in patients with complete panhypopituitarism (Fig. 2). A significant and rapid increase in plasma Δ4 ADIONE levels was observed after oral DHEA administration ($P < 0.01$). With 50 mg, plasma Δ4 ADIONE levels increased after 3 h to physiological levels observed in normal men and premenopausal women (6.2 ± 0.7 nmol/L). With the 200 mg dose, the peak occurred after 2 h and was 5-fold more important (23.0 ± 2.6 nmol/L). Plasma T levels after treatment (1.5 ± 0.3 nmol/L) with 50 mg of DHEA were, after 3 h, within the normal values observed in premenopausal women. A 7-fold increase in plasma T levels (6.9 ± 1.3 nmol/L) compared with the 50 mg dose was observed 2 h after a 200 mg dose of DHEA. The rise in plasma DHT levels was small in both groups of patients and occurred 3 h and 4 h after the 50 and the 200 mg doses respectively.

Plasma and urinary androgen glucuronide metabolites

Plasma ADTG and ADG levels were undetectable or barely detectable in patients with panhypopituitarism (Fig. 3A). A prompt and dramatic increase of ADTG levels was observed after DHEA ingestion. After a 50 mg DHEA dose, plasma ADTG levels increased after 1 h, from 0.1 ± 0.08 to 342 ± 63 nmol/L, within the normal range of healthy subjects. With the dose of 200 mg, the peak was 10-fold more important than with the 50 mg dose (3276.0 ± 635.0 nmol/L) and occurred after 3 h. A parallel increase of ADG was observed. However, plasma ADG levels were two orders of magnitude below those of ADTG, 7.1 ± 1.3 and 45 ± 7.8 nmol/L, after the 50 and the 200 mg doses respectively.

In placebo treated patients, urinary ADG was extremely low (5 ± 2 μmol/24 h) (Fig. 3B). After ingestion of 50 mg of DHEA, ADG reached levels (85 ± 7 μmol/24 h) seen in

TABLE 2. Plasma levels of sex steroids and thyroid hormones (basal levels), F, and pituitary (peak after GnRH, CRH, and GHRH) hormones in ten patients at the time of diagnosis of panhypopituitarism

Patient no.	T	E_2	FT_4	LH	FSH	F	ACTH	GH	PRL	TSH
				GnRH 100 μg, iv		CRH 100 μg, iv		GHRH 100 μg, iv	TRH 100 μg, iv	
1	ND	26	2.0	0.5	3.0	16	0.5	0.4	56	0.1
2	0.17	22	3.9	1.6	2.2	32	1.7	1.6	120	1.3
3	0.17	27	3.1	1.9	3.2	43	1.1	0.7	138	0.9
4	ND	20	3.0	2.1	2.8	23	2.0	1.3	92	1.7
5	ND	ND	2.6	0.5	0.7	20	0.7	0.6	60	0.2
6	ND	34	3.2	1.2	1.8	65	2.0	0.8	163	1.2
7	0.17	20	2.9	0.9	2.6	27	0.8	2.0	112	0.9
8	ND	30	2.5	0.6	2.2	62	1.6	1.6	98	0.6
9	ND	39	4.2	2.0	6.0	52	1.9	3.2	610	9.2
10	ND	19	2.3	1.2	2.0	46	1.2	2.3	130	1.8
Normal basal values	0.5–2.6[a] nmol/L	37–150[b] pmol/L	11–24 pmol/L	4–8[c] IU/L	4–9[c] IU/L	250–650 nmol/L	2.2–11.0 pmol/L	0.4–50 μg/L	<600 mIU/L	0.2–3.5 mIU/L

ND, not detectable.
[a] Plasma T levels in women.
[b] Plasma E_2 levels in men.
[c] Values in premenopausal women in the early follicular phase.

normal young women but remained below normal values observed in young men. After 200 mg, 24-h urinary ADG levels were 5-fold above the levels observed with 50 mg (450 ± 50 μmol/24 h).

Plasma estrogens

Basal plasma E_1 and E_2 levels were very low. A dose dependent increase in both estrogens was observed after DHEA administration after 3 h and 4 h respectively (Fig. 4). The peak of plasma E_2 levels was higher than that observed with E_1. With 50 mg of DHEA, plasma E_2 levels (87 ± 7 pmol/L) were within the normal range observed in men. With a 200 mg dose, plasma E_2 levels were within the normal range observed in the early follicular phase (294 ± 60 pmol/L).

Discussion

In patients with panhypopituitarism, plasma DHEA and DHEAS levels were not detectable. This deficiency associated with the absence of sex steroid secretion suggests that this model may be of interest for studying the metabolism and role of DHEA in humans. The administration of a 50 mg dose restored plasma levels of DHEA to that observed in young individuals. In contrast, the 200 mg dose induced supraphysiological plasma levels. This has been previously reported even with a 100 mg dose (15). The dramatic increase of plasma DHEAS in these patients reflected the important extraadrenal (*e.g.* hepatic) sulfotransferase activity (16–18). This result also indicates that, in opposition to what has been reported in rodents, the expression of this hepatic enzyme in humans with pituitary deficiency is at least in part independent of growth hormone (19).

The increase of plasma Δ5 ADIOL levels was small. In contrast, an increase in plasma Δ4 ADIONE of similar magnitude to that of plasma DHEA levels was observed within hours of DHEA administration. This increase implied an extensive conversion of the Δ5 steroid into the Δ4 derivative as previously reported (20). In patients with panhypopituitarism, this process clearly confirms the physiological relevance of the extraadrenal and extragonadal 3β-hydroxysteroid dehydrogenase activity (3β-HSD) and indicates the persistent expression of the peripheral 3β-HSD isozyme (type I) despite the absence of pituitary trophic hormones (21). In addition, Δ4 ADIONE was significantly reduced into the active sex steroid T by the peripheral, extragonadal, 17β-hydroxysteroid dehydrogenase (isozyme type 2) (22, 23). Thus, the administration of a 50 mg dose of DHEA restored plasma T to levels observed in young women, whereas with the 200 mg dose, plasma T levels increased, reaching levels observed in normal men. Although, the increase of plasma DHT was modest at both doses of DHEA, the physiological importance of both the 5α-reductase and the 3α-ketoreductase metabolic pathways in these patients was indicated by the large conversion of DHEA into ADTG and ADG (24, 25). In patients receiving the 50 mg replacement dose, the increase of plasma and urinary ADG to levels observed in normal women is consistent with previous reports, indicating that DHEA is a main precursor of ADG in women (26). In contrast, this dose failed to restore plasma and urinary ADG into the range of normal men, confirming that T is the principal source of this metabolite in men (27, 28). On the other hand, the plasma ADTG levels obtained were two orders of magnitude above those of ADG. This difference, associated with the small increase of Δ5 ADIOL and higher Δ4 ADIONE levels than T levels, indicates that in these patients DHEA administered orally was preferentially converted into C19 17-keto steroids than in the 17-keto reduced corresponding metabolites. Finally, there occurred a significant and dose dependent conversion of DHEA into estrogens by the widely distributed extragonadal aromatase (29). In opposition to DHEA metabolism into C19 metabolites, DHEA conversion to estrogens was preferentially directed into the 17-keto reduced pathway. This result suggests that, in contrast with *in vitro* reported data (30), the peripheral 17β-HSD type 2 preferentially catalyzes the reductive reaction when estrogens are used as substrates (22). Indeed, the two gonadal isozymes, 17β-HSD type 1 and 17β-HSD type 3, which preferentially catalyze the reductive reaction, are

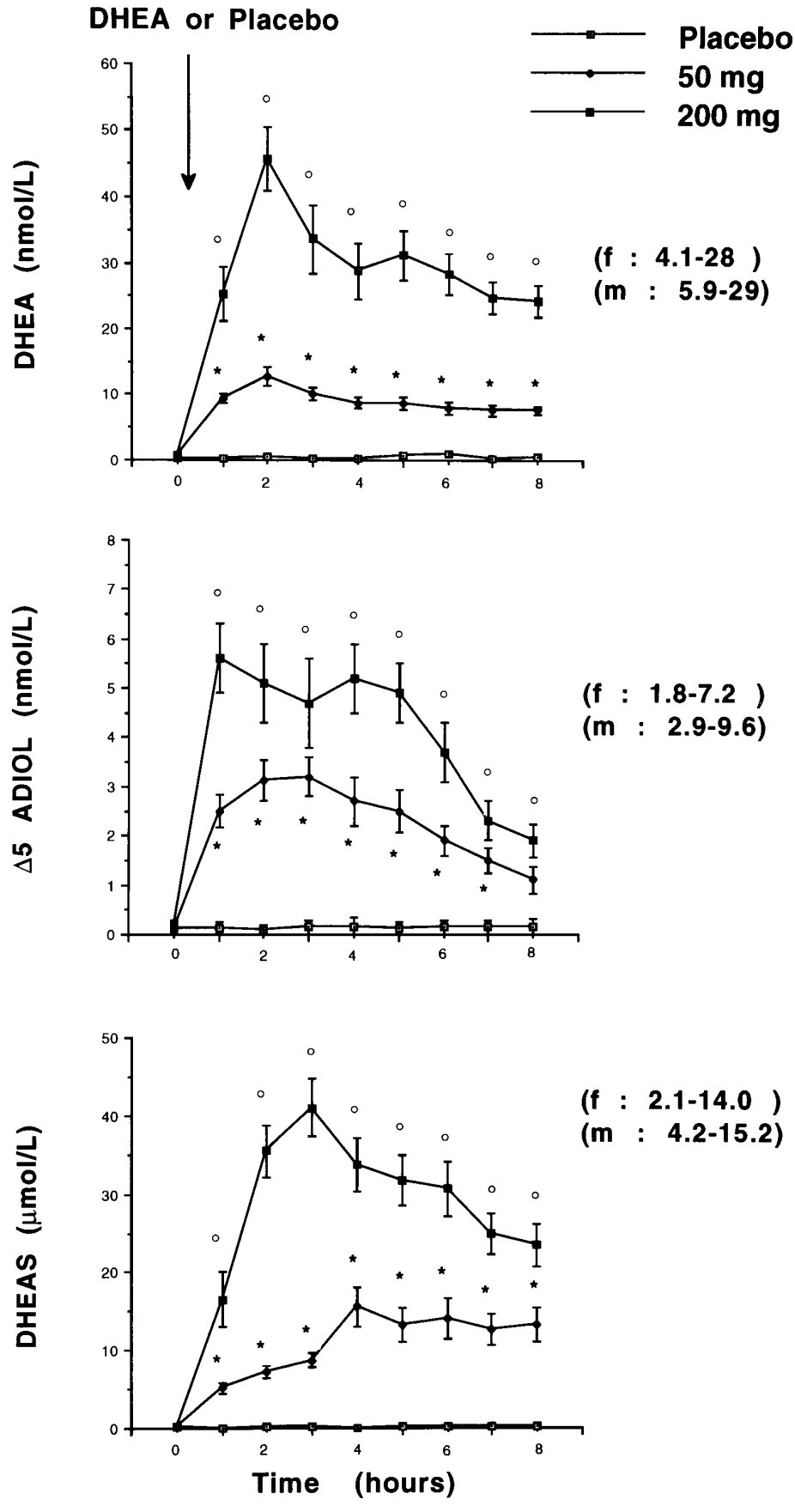


FIG. 1. Mean (± SE) plasma Δ5 steroids in patients with panhypopituitarism treated with placebo or a single oral dose of DHEA (50 mg or 200 mg). * indicates $P < 0.01$ compared with placebo. ○ indicates $P < 0.01$ compared with 50 mg. In parentheses, the normal range in young individuals; f = women in the early follicular phase; m = men.

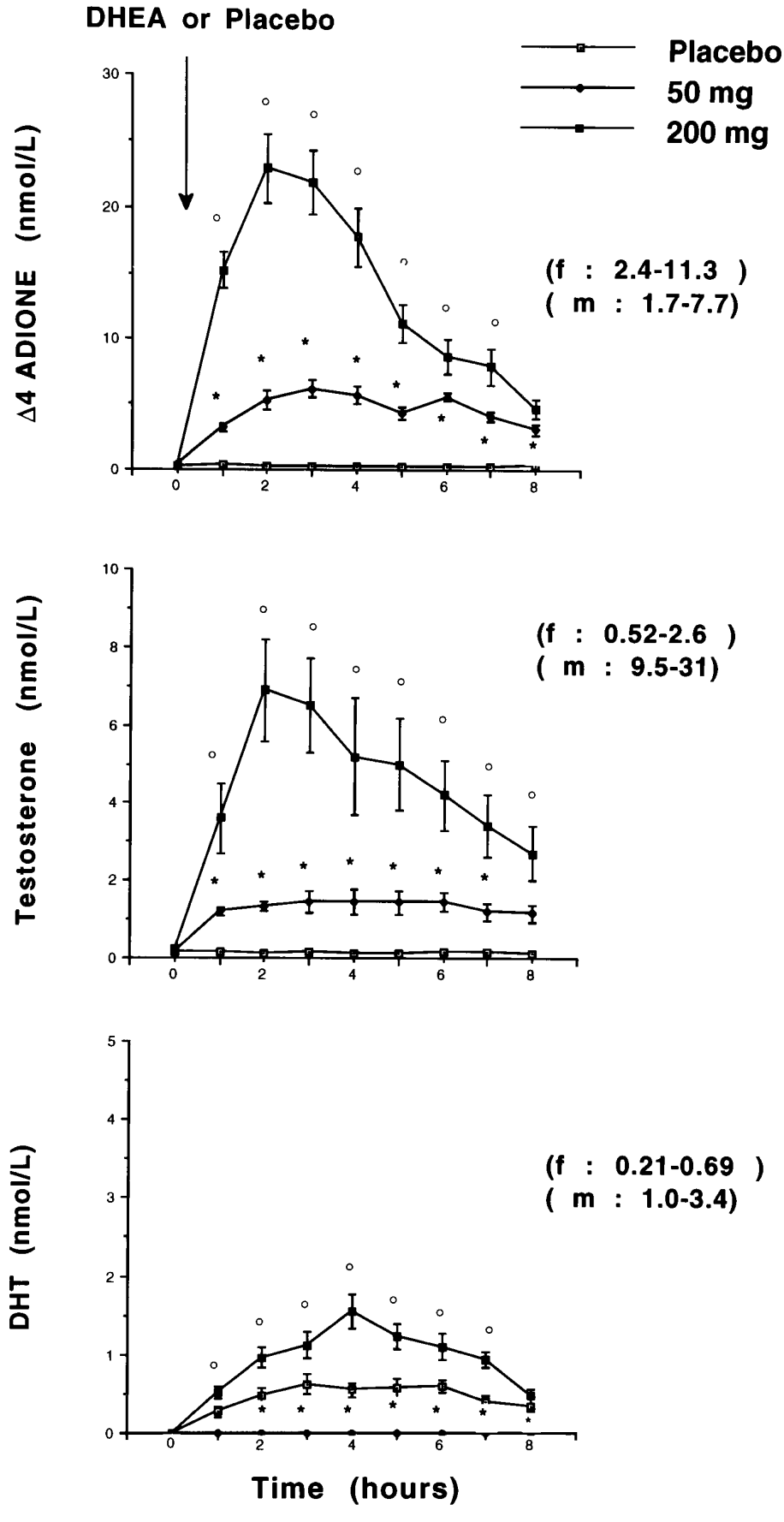


FIG. 2. Mean (± SE) plasma androgens in patients with panhypopituitarism treated with placebo or a single oral dose of DHEA (50 mg or 200 mg). * indicates $P < 0.01$ compared with placebo. ○ indicates $P < 0.01$ compared with 50 mg. In parentheses, the normal range in young individuals; f = women in the early follicular phase; m = men.

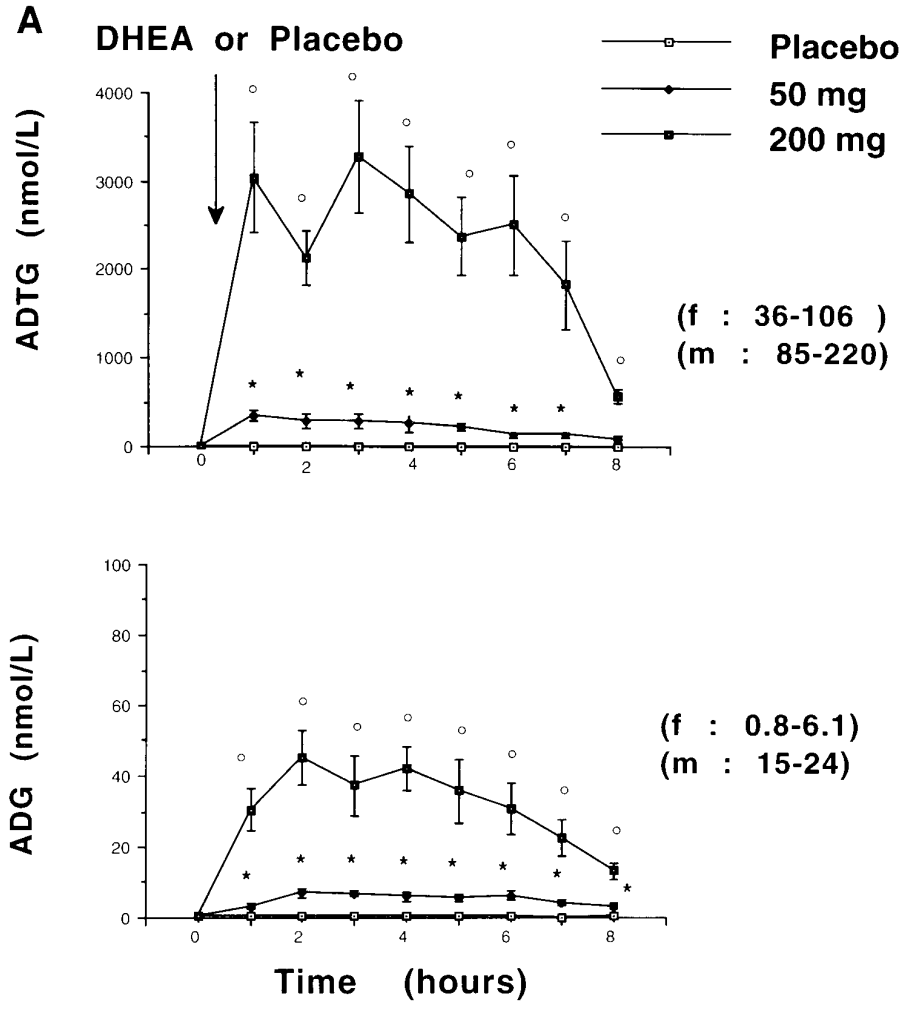
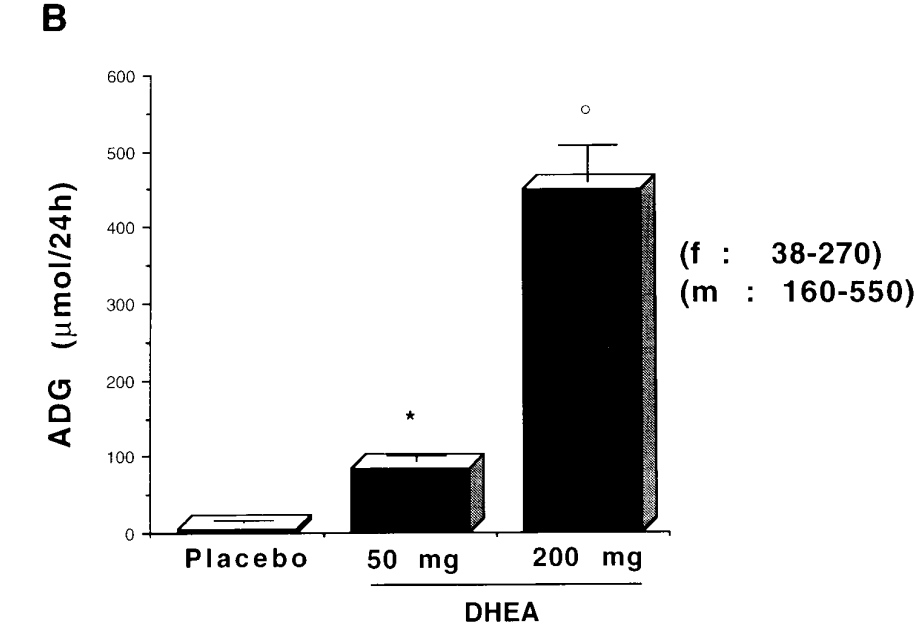


FIG. 3. Mean (± SE) plasma (A) and urinary (B) androgen glucuronide metabolites in patients with panhypopituitarism treated with placebo or a single oral dose of DHEA (50 mg or 200 mg). * indicates $P < 0.01$ compared with placebo. ○ indicates $P < 0.01$ compared with 50 mg. In parentheses, the normal range in young individuals; f = women in the early follicular phase; m = men.



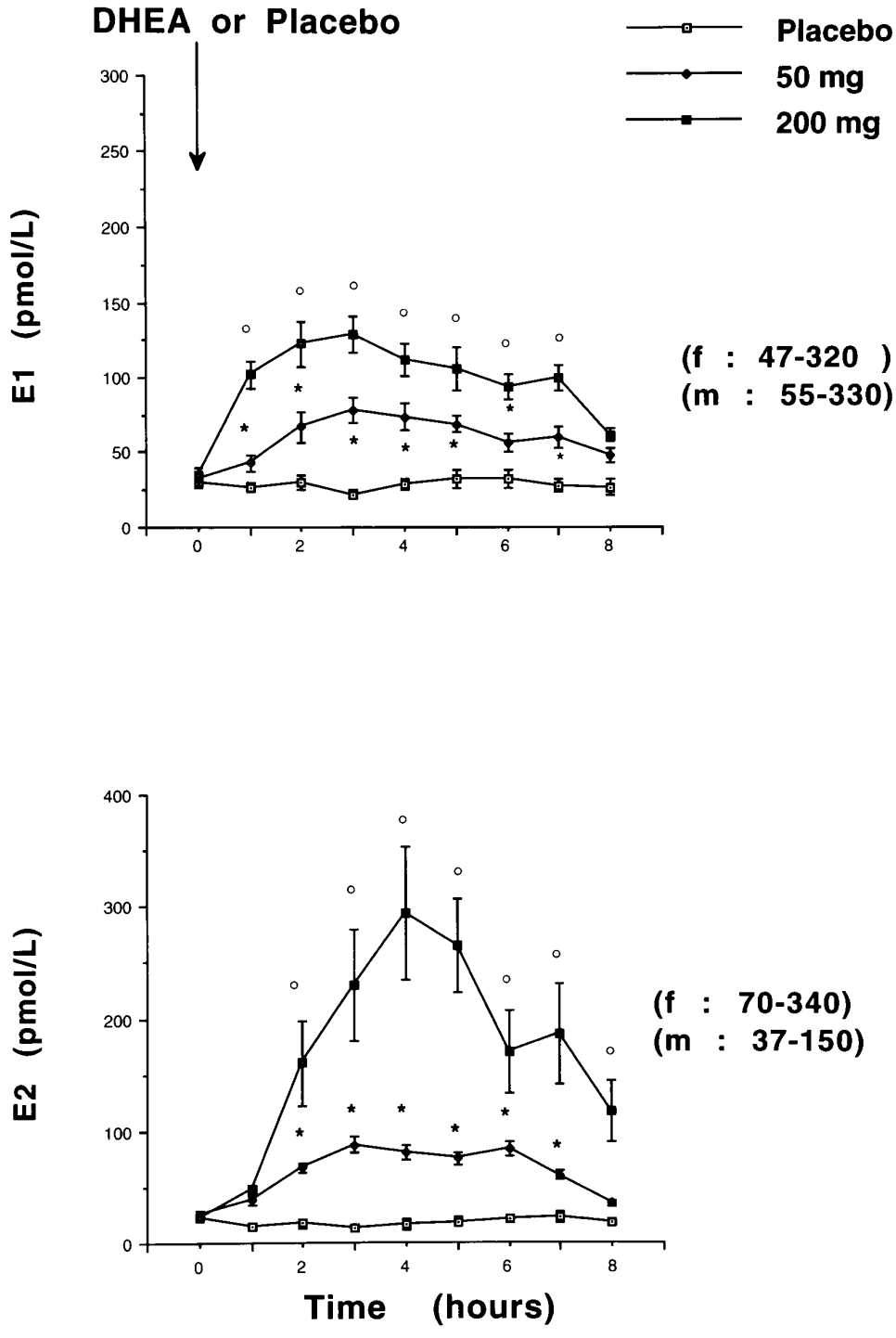


FIG. 4. Mean (± SE) plasma estrogens in patients with panhypopituitarism treated with placebo or a single oral dose of DHEA (50 mg or 200 mg). * indicates $P < 0.01$ compared with placebo. ○ indicates $P < 0.01$ compared with 50 mg. In parentheses, the normal range in young individuals; f = women in the early follicular phase; m = men.

not expressed in these patients lacking gonadotropin secretion.

The metabolism of DHEA into potentially active sex steroids can occur inside many cells containing androgen and/or estrogen receptors that may interact with them. This is the case in adipose tissue, bone, muscle, breast, prostate, skin, brain, and particularly in the liver where the metabolism of DHEA is quantitatively important (31). This intracrine mechanism may explain many androgenic and estrogenic properties of DHEA observed *in vivo* (7, 32). However, the present study clearly demonstrates that these active DHEA metabolites may be released into the circulation and reach target tissues lacking DHEA metabolizing enzymes. Therefore, estrogenic and androgenic effects of DHEA can be mediated by a classic endocrine pathway.

In the absence of a clearly demonstrated peripheral DHEA receptor, a number of previously reported effects assigned to this steroid in humans could be related to its conversion to sex steroids. Conversion of DHEA into potent androgens probably accounts for the increased index of sebum secretion

reported in postmenopausal women as well as acne in addisonian female patients treated with the 50 mg DHEA replacement dose (7). In addition, the high androgen environment induced by pharmacological doses of DHEA could explain the previously reported induction of an atherogenic lipid profile and an insulinoresistant state in postmenopausal women (4). At both replacement and pharmacological doses of DHEA, the active steroid E_2 reached levels compatible with the occurrence of estrogenic actions. This result could explain the number of beneficial effects induced by DHEA in postmenopausal women, like vaginal epithelium maturation, decrease of fasting insulin levels, and increase of bone mass density and plasma osteocalcin levels (7, 33, 34). The increase in IGF-I plasma levels previously reported after DHEA administration may also be explained by its conversion into sex steroids (5, 35, 36).

The ability of DHEA to undergo biotransformation into potent androgens and estrogens implies that hormonodependent diseases like prostate, endometrium, or breast cancer should be carefully ruled out before any long-term administration.

In conclusion, 1) panhypopituitarism represents a convenient model to assess in humans the metabolism and actions of DHEAS; 2) the present report shows that, in the absence of adrenal and gonadal steroids, oral DHEA is mainly converted into Δ4 derivatives, which in turn are metabolized into active sex steroids. This biotransformation may explain some reported beneficial actions of DHEA; 3) long-term studies are needed to carefully assess in panhypopituitarism the therapeutic effects of DHEA in addition to the usual sex hormone replacement therapy.

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